Remarks

Claims 1-3 and 7 were pending prior to this Response. By the present communication, no claims have been canceled, claims 17-21 have been added, and claim 1 has been amended to define Applicants' invention with greater particularity. Support for amended claim 1 may be found, among others, at page 21, lines 5-7, of the specification as filed. Support for new claims 17-21 may be found, among others at page 34, lines 1-3 and lines 17-18 of the specification as filed. The amendments do not raise any issues of new matter and the amended claims do not present new issues requiring further consideration or search. Accordingly, upon entry of the present amendment, claims 1-3, 7, and 17-21 will be pending in this application.

Rejection under 35 U.S.C. § 112

Applicants respectfully traverse the rejection of claims 1-3 and 7 under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the written description requirement. Specifically, the Office Action alleges that the limitation "wherein the toxin is 95% pure" is new matter. In addition, the Office Action indicates that the "original disclosure supports 95% purity level for the natural toxin rather than the attenuated toxin" (Office Action, page 3). Without acquiescing to the reasoning offered by the Office, and in order to expedite prosecution of the instant application, Applicants have amended claim 1 to recite that the purified and unattenuated toxin is 95% pure. Accordingly, withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 103

Applicants respectfully traverse the rejection of claims 1, 3, and 7 under 35 U.S.C. §103(a) as allegedly unpatentable over Germanier, et al (hereinafter "Germanier"). The recent U.S. Supreme Court decision in the KSR International v. Teleflex Inc. (82 USPQ2d 1385), modified the standard for establishing a *prima facie* case of obviousness. Under the KSR rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to be shown. Second, the combination has to suggest a reasonable expectation of success. Third, the prior art reference or combination

has to teach or suggest all of the recited claim limitations. Factors such as the general state of the art and common sense may be considered when determining the feasibility of modifying and/or combining references.

The Office Action alleges that Germanier teaches a purified an attenuated cholera toxin having a residual toxic activity of less than 1/2000 that of the natural toxin, attenuated by incubation at 30 to 40 degrees Celsius with formalin, wherein the amino acid sequence of the toxin has not bee modified. According to the Office Action, the difference between the claimed toxin and the toxin of Germanier is that it is not readily apparent if the purified and attenuated toxin of Germanier is 95% pure. Without acquiescing to the reasoning offered by the Office, and in order to expedite prosecution of the instant application, Applicants have amended claim 1 to require specific steps of obtaining the purified an attenuated toxin.

Applicants submit that Germainer's toxin is subjected to heat treatment at 60°C for 25 minutes prior to the formalin treatment (see Germanier, page 1693, left column, "Detoxification of cholera toxin"), in order to *convert the purified toxin into a procholeragenoid.* In contrast, Applicants' purified toxin is directly subjected to formalin treatment *without* converting the purified toxin into a procholeragenoid.

Applicants further submit that the structure of Germanier's procholeragenoid differs from that of the present invention's purified (unheated) toxin, as evidenced by, for example, FIG. 31 of Germanier. The data of gel electrophoresis demonstrates that the electrophoretic mobility of cholera toxin is significantly reduced by incubation at 60°C (please compare lane 1 with lanes 2-7 of "FIG 1" of Germanier). This mobility shift reflects the difference in molecular weight, *i.e.*, the structural difference, between *unheated cholera* toxin and *procholeragenoid.* Similarly, the immunoelectrophoretic data of FIG. 4 shows that the position of the band of unheated toxin (lane "CT") is clearly distinguishable from those of heated toxins (*i.e.*, procholeragenoids) (lanes 5, 15, and 25). As such, this data also supports the structural difference between unheated cholera toxin and procholeragenoid.

More specifically, the heat treatment of Germanier produces a *polymer* (see abstract and "Detoxification of cholera toxin" on page 1694 of Germanier), which is formed through aggregation of CT (see the first paragraph in "Discussion" on page 1669 of Germanier). The

structure of Germanier's procholeragenoid clearly differs from that of the natural cholera toxin (see FIGS. 1 and 3 of Germanier). Similarly, formalin-treated procholeragenoid is structurally distinguishable from CT (see FIG. 4 of Germanier). Thus, even if formalin treatment is performed both in the present invention and in Germanier, the structure of the final product (*i.e.*, attenuated toxin produced by formalin treatment) of the present invention differs from that of Germanier.

Applicants further respectfully direct the Examiner's attention to the following points. In Germainer, the term "detoxification" (which corresponds to "attenuation" of the present invention) includes both heat treatment and formalin treatment (see p. 1693, left column, "Detoxification of cholera toxin."). Applicants submit that one of skill in the art would understand that "Detoxification/attenuation" is generally categorized as "chemical detoxification/attenuation" (such as by treatment with formalin, β-propiolactone, ethanol, etc.) and "physiochemical detoxification/attenuation" (such as with pH, temperature, light, γ-ray, etc.). Thus, Germanier's heat treatment at **60°C** for 25 minutes prior to formalin treatment is interpreted as "physiochemical *attenuation*." This attenuated condition is not included instant step (b) of claim 1 (*i.e.*, attenuating ... by incubation... at 5°C to 40°C). Accordingly, the purified and attenuated toxin of claim 1 is clearly distinguishable from Germanier's toxin.

Accordingly, Applicants respectfully submit that Germanier fails to disclose each and every limitation of the claimed invention. As such, even if one of skill in the art were to purify the attenuated toxin of Germanier, Applicants submit that the resulting modification would *not* ultimately the attenuated toxin of the instant invention since Germanier treats a procholeragenoid with formalin, while the instant invention requires that a purified toxin is directly treated with formalin (*i.e.,* an unheated toxin is treated with formalin). Withdrawal of the rejection is respectfully requested.

Applicants respectfully traverse the rejection of claim 2 under 35 U.S.C. §103(a) as allegedly unpatentable over Germanier, as applied to claim 1, in view of Douce, et al. (hereinafter, "Douce"). The arguments provided above distinguishing Germanier from the claimed invention apply equally and are incorporated here. The Office Action relies upon Douce

for allegedly disclosing the substitution, insertion, deletion or addition of one or more amino acid residues of a toxin to modify the adjuvanticity and immunogenicity of the toxin while retaining the existing serine, glutamic acid and lysine residues. However, Douce fails to cure the above-discussed defects of Germanier.

Accordingly, even if one were to combine Germanier with Douce, the resulting combination would not be *prima facie* obvious over the claimed invention since the combined references do not disclose each and every claim limitation. Withdrawal of the rejection is respectfully requested.

Conclusion

In summary, for the reasons set forth herein, Applicants maintain that the claims clearly and patentably define the invention and respectfully request that the Examiner withdraw all rejections and pass the application to allowance. If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

The Commissioner is hereby authorized to charge $1050.00 as payment for the Petition for Three-Month Extension of Time fee to Deposit Account No. 07-1896. Additionally, the Commissioner is hereby authorized to charge any other fees that may be due in connection with the filing of this paper, or credit any overpayment to Deposit Account No. 07-1896.

Respectfully submitted,

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